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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/203,078	12/01/1998	SHUYUAN ZHANG	INRP:081	3754

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EXAMINER

FOLEY, SHANON A

ART UNIT PAPER NUMBER

1648

DATE MAILED: 10/03/2003

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Please find below and/or attached an Office communication concerning this application or proceeding.

# Office Action Summary

Application No.

09/203,078

Applicant(s)

ZHANG ET AL.

Examiner

Shanon Foley

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

## Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

## Status

- 1) ☒ Responsive to communication(s) filed on 28 February 2002.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

## Disposition of Claims

- 4) ☒ Claim(s) 1-29 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-29 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

## Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on \_\_\_\_\_ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

## Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
  - ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

## Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 19, 22.
- 4) ☐ Interview Summary (PTO-413) Paper No(s). \_\_\_\_\_.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: \_\_\_\_\_.

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### **DETAILED ACTION**

Applicant timely responded to the first action on the merits of 9/13/01. However, due to inadvertent clerical errors, the Office has not timely responded to applicant's amendment submitted 2/28/02. The examiner regrets any inconvenience applicant experiences due to this delay.

In paper no. 21, applicant cancelled claims 30-43, amended claims 3, 18 and 23-25. Claims 1-29 are pending and under consideration.

Applicant's arguments and the declaration submitted by Shawn Gallagher convincingly points out that the invention is not drawn to different cell cycle phases, but growth phases of the culture. Upon reconsideration, new grounds of rejection are established.

#### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1-3, 8-25 and 29 rejected under 35 U.S.C. 103(a) as being unpatentable over Huyghe et al. (C44), Zhang et al. (6,143,290) and Leu et al. (US 6,194,210).

Claims 1-3 and 8-29 are drawn to a method of preparing a recombinant adenovirus by allowing a culture of producer cells (293) to attach to a culture surface, infecting the producer cells with recombinant adenovirus between late-log and stationary phase. The medium is at least partially recirculated during the infection step. The adenovirus is purified by a variety of chromatographic separations and placed into a pharmaceutically acceptable carrier. The

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adenovirus is replication-deficient, lacks a portion of the E1 region and encodes p53 from a promoter. The adenovirus is harvested by steps other than freeze-thaw and the harvested adenovirus has the following listed in claim 29.

Huyghe et al. teach a method for purifying a recombinant adenovirus encoding p53 from 293 cells by a variety of chromatographic techniques, including ion exchange, see the abstract, first paragraph under “materials and methods”, and the section bridging pages 1407-1408. A monolayer of 293 cells were plated and attached to the surface before infection with adenovirus mixed with fresh culture medium. Although Huyghe et al. do not teach the specific seeding densities recited in claims 10-12, it is conventional in the cell culture art to seed cells at an appropriate density within a flask to possess enough space between the cells for growth without plating too thinly so that the cells would not meet, see the Freshney reference provided by applicant for example. Huyghe et al. do not teach a promoter driving p53 gene expression.

Zhang et al. teach a method for expressing an adenovirus encoding p53 that is under the control of an SV40 promoter. Since all of the promoters listed in claim 25 are used conventionally for gene expression in adenovirus, all would be obvious alternatives to the promoter used by Zhang et al. to one of ordinary skill in the art at the time the invention was made.

As applicant has pointed out, none of the references cited previously teach infecting cells at late-log phase.

However, Lau et al. teach a method of producing large quantities of virus by allowing uniform attachment of cells, growing the cells to late-log phase with medium replenishment to provide adequate cell nutrition and infecting the cells at late-log phase and harvesting the virus,

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see column 11, lines 18-column 12, line 9 and claims 1 and 4. One of ordinary skill in the art at the time the invention as made would have been motivated to have propagated the adenovirus of Huyghe et al. and Zhang et al. with the cell culture method steps of infection, taught by Lau et al. to increase the amount of adenovirus produced in cell culture. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of growing the adenovirus of Huyghe et al. and Zhang et al. with the cell culture method steps taught by Lau et al. because Lau et al. teach that a wide range of viruses may be propagated to generate vaccines using the method steps, see column 5, lines 29-32. Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art, absent unexpected results to the contrary.

Claim 29 requires the adenovirus to possess certain characteristics, described in product-by-process language. Since the characteristics of an adenovirus are determined by the viral genome, a virus has the same characteristics (or very similar characteristics) regardless of the method used to produce a purified suspension of viruses. Since both applicant's method and the reference method produce purified p53 recombinant adenoviruses, the virus products are seen as identical, or so similar as to be obvious variants. The Patent Office does not have facilities to produce applicant's product-by-process virus and compare it to other, similar prior art products.

Claim 4 is rejected under 35 U.S.C. 103(a) as being unpatentable over Huyghe et al. (C44), Zhang et al. (6,143,290) and Leu et al. (US 6,194,210) as applied to claims 1-3, 8-25 and 29 above, and further in view of Garnier et al. (C26) or Perrin et al. (C73) for reasons of record.

Applicant argues that neither reference teach or suggest maintaining a low concentration of glucose. However, claim 4 is only drawn to perfusing the producer cells only a portion of the

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time and does not recite glucose concentration levels. Therefore, it is maintained that the references teach all of the limitations and provide a motivation for perfusing with a reasonable expectation of success, absent unexpected results to the contrary.

Claims 26-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Huyghe et al. (C44), Zhang et al. (6,143,290) and Leu et al. (US 6,194,210) as applied to claims 1-3, 8-25 and 29 above, and further in view of Graham et al. (C7).

The claims are drawn to lysing the producer cells with a detergent by means other than freeze-thaw. Graham et al teach that 5% sodium deoxycholate can be used to disrupt cells without disrupting adenovirus virions, see page 119. Therefore it would have been obvious to use deoxycholate or another detergent as an alternative method to lyse the infected cells.

#### ***Allowable Subject Matter***

Claims 5-7 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. As applicant points out, the prior art does not teach or suggest perfusion rates to maintain a low concentration of glucose.

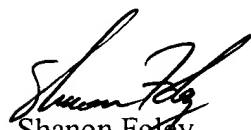
#### ***Conclusion***


Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shanon Foley whose telephone number is (703) 308-3983. The examiner can normally be reached on M-F 9:00-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on (703) 308-4027. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

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Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

  
Shanon Foley

  
JAMES HOUSEL 10/1/03  
SUPERVISORY PATENT EXAMINER  
TECHNOLOGY CENTER 1600